(A) an amount of an agent that is effective to induce apoptosis or increase a rate of apoptosis in a target cell or tissue; and

(B) an amount of a tyrosine kinase inhibitor that is effective to reduce resistance to induction of apoptosis or resistance to the increased rate of apoptosis in the target cell or tissue expressing a mutant EGFR gene, the resistance being mediated by a mutant EGFR.

Summary of Final Office Action

1. Claims 1-16 stand rejected under 35 U.S.C. 112 (first paragraph) as allegedly not meeting the written description requirement.

2. Claims 1-7 stand rejected under 35 U.S.C. 102(a) as allegedly being anticipated by Nagene *et al.* (1998) Proc. AACR Spec. Conf.

3. Claims 1-16 stand rejected under 35 U.S.C. 103 as allegedly being obvious over Han *et al.* (1996) Cancer Res. 56, 3859-3861 in view of Reed *et al.* (U.S. Patent 5,831,066) in further view of Tsai *et al.* (1996) Cancer Res. 56, 937-1177.

Rejection under 35 U.S.C. 112 (first paragraph)

Claims 1-16 stand rejected under 35 U.S.C. 112 (first paragraph) for allegedly not meeting the , written description requirement. The Examiner contends that there is no support for "an amount of a tyrosine kinase inhibitor that is synergistically effective" in accordance with claims 1, 9 and 13 (see Office Action at page 2, lines 17-19). Without attesting to the merits of this rejection, Applicants have amended the claims to remove this term in order to put the claims in better condition for appeal. The rejection is therefore moot and withdrawal of the rejection is requested.

Rejection under 35 U.S.C. 102(a)

Claims 1-7 were rejected under 35 U.S.C. 102(a) as being anticipated by Nagene *et al.* As stated in Applicant's previous response (filed December 6, 2001), the term "others" in 35 U.S.C. 102(a) refers to any entity that is different from the inventive entity. In this case, although authorship of the abstract includes only three of the present inventors, the disclosure at issue that was presented at the meeting resulted from a collaboration including all five of the named inventors of the instant application. In order to overcome this rejection, Applicants file concurrently with this response a Declaration of under 37 C.FR. 1.132 of Webster K. Cavenee. In the Declaration, Dr. Cavenee attests that, to the extent that the abstract teaches a concept claimed in the instant application, the authors of the abstract derived their knowledge from the inventive entity of this application. Accordingly, the disclosure in the abstract and the presentation at the AACR Special Conference was not by "others" as required by 35 U.S.C. 102(a). In view of these remarks and the attached Declaration, Applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. 103

Claims 1-16 stand rejected under 35 U.S.C. 103 for allegedly being obvious over Han *et al.* in view of Reed *et al.* in further view of Tsai *et al.* Applicants respectfully maintain that there is no motivation to combine the cited references and that the claimed invention is not obvious.

Applicants have unexpectedly discovered that the expression of mutant EGFR genes in cells can suppress the apoptosis inducing activity of chemotherapuetic agents and further discovered methods for the modulation of the apoptosis-inhibiting effects of mutant EGFR gene products to enhance the efficacy of therapies which induce apoptosis. The Tsai *et al.* reference on which the Examiner relies for motivation teaches that certain tyrosine kinase inhibitors enhance the sensitivity of certain cancer cells to chemotherapeutic agents. This reference does not address the modulation of apoptosis in cells or tissues having mutant EGFR genes. As such, this reference does not imply nor suggest methods for the modulation of the apoptosis-inhibiting effects of mutant EGFR gene products to enhance the efficacy of therapies which induce apoptosis.

The Examiner acknowledges this position but contends that it is not necessary that any of the cited references disclose that a mutant EGFR gene is involved in modulation of apoptosis in a tumor cell. Specifically, the Examiner states that "it is not necessary to the Examiner's *prima facie* [obviousness] case that any of the references disclose that a mutant EGFR gene is involved in modulation of apoptosis in a tumor cell, but only that the references reasonably would have suggested to one ordinarily skilled in the art to what Applicant now claims" (see Office Action at page 4, lines 14-19). Based on this statement, the Examiner's position is that there is no disclosure in the cited references establishing a relationship between apoptosis and a mutant EGFR gene. The Examiner therefore appears to be relying on some other type of motivation for combining these references that is not clearly stated in the Office Action.

The Examiner states that the disclosure in Tsai *et al.* of the ability of selective tyrosine kinase inhibitors to enhance the sensitivity of certain chemotherapeutic cancer agents would be sufficient motivation for the skilled artisan to expect the combination of these agents to modulate the apoptosis-inhibiting effect of the mutant EGFR gene (see Office Action at page 4, lines 8-14). Applicants disagree because given the broad number of chemotherapeutic agents with distinct mechanisms of action, the skilled artisan at the time of the invention would not have been motivated or even had an expectation of success with regard to the claimed method directed to the combination of two specific classes of

compounds (*i.e.*, a tyrosine kinase inhibitor with the claimed properties and a second agent which induces apoptosis or the rate of apoptosis). Applicants bring the attention of the Examiner that chemotherapeutic agents fall in many different drug categories with multiple and distinct mechanisms of action. Even given the disclosure of Tsai *et al.*, the skilled artisan would not have expected a single class of compounds (*i.e.*, tyrosine kinase inhibitors) to be effective in combination with all chemotherapeutic agents let alone the specific class of agents recited in the claims. Applicants therefore submit that the Examiner has not established a *prima facie* case of obviousness because she has not identified why the disclosure of a Tsai *et al.* is sufficient to provide motivation to the skilled artisan to combine the teachings of Reed *et al.* and Han *et al.* to arrive at the claimed invention. In the absence of such an explanation, withdrawal of this rejection would be appropriate.

Applicants respectfully request reconsideration of the subject application in view of the amendments to the claims and the above remarks and withdrawal of the remaining rejections. It is respectfully submitted that this application is now in condition for allowance. Should the Examiner believe it to be useful, an interview with the Examiner is respectfully requested in order to discuss the foregoing claims.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "version with markings to show changes made" as required. If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted
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Dated: **April 28, 2003**
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